STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 145196

TO: Marcela Cordero Garcia Location: REM-3C18 Monday, April 18, 2005 Art Unit: 1654 Case Serial Number: 10/659179	From: David Schreiber Location: Biotech-Chem Library Remsen E01A61 Phone: 571-272-2526 David.Schreiber@uspto.gov

Search Notes

149196

STIC-Biotech/ChemLib

From: Unknown@Unknown.com
Sent: Tuesday, March 29, 2005 2:59 PM
To: STIC-Biotech/ChemLib
Subject: Generic form response

ResponseHeader=Commercial Database Search Request

AccessDB#= _____

LogNumber= _____

Searcher= _____

SearcherPhone= _____

SearcherBranch= _____

MyDate=Tue Mar 29 14:58:00 EST 2005

submitto=Biotech01@uspto.gov

Name=Marcela M Cordero Garcia

Empno=80381

Phone=2-2939

Artunit=1654

Office=REM3C18

Serialnum=10/659,179

PatClass=514/2

Earliest=9/9/03

Searchtopic=Please search in NPL and MARPAT:

1)MULTIVALENT SALTS of Cbz-Phe-Pro-Mpg-B(OH)2
where:
Cbz= benzyloxycarbonyl
Mpg=3-methoxypropylglycine (a hydrophobic unnatural amino acid)
(if too many hits, please use "hemicalcium salt" instead of multivalent salt)

2)IF only Applicant's own work found, please search broad claim:
A salt of a pharmaceutically acceptable multivalent metal and an organoboronic acid inhibitor of thrombin having a neutral thrombin S1-binding moiety linked to a hydrophobic thrombin S2/S3-binding moiety.

Thanks,

Marcela

****
STAFF USE ONLY

Searcher: D. Schreiber
Searcher Phone: 2-2526
Date Searcher Picked up: 4/7
Date Completed: 4/18
Searcher Prep/Rev. Time: 17
Online Time: 72

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Type of Search

NA#:_____ AA#:_____
Interference:____ SPDI:___
S/L:_____ Oligomer:_____
Encode/Transl:_____
Structure#:__1__ Text:___
Inventor:____ Litigation:___

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Vendors and cost where applicable
STN: 324.16
DIALOG:_____
QUESTEL/ORBIT:_____
LEXIS/NEXIS:_____
SEQUENCE SYSTEM:_____
WWW/Internet:_____
Other(Specify):_____

Comments=Please also do an inventor search:
DEADMAN, JOHN JOSEPH; MADGE, DAVID JONATHAN; DOLMAN, MARK; KAKKAR, SANJAY KUMAR; KENNEDY, ANTHONY JAMES; COMBE-MARZELLE, SOPHIE MARIE;
CHAHWALA, SURESH BABUBHAI; BOUCHER, OLIVER VIMPANY ARNOLD

send=SEND

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STAFF USE ONLY

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FILE 'HCAPLUS' ENTERED AT 09:05:38 ON 18 APR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 18 Apr 2005  VOL 142 ISS 17
FILE LAST UPDATED: 17 Apr 2005  (20050417/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L21             STR
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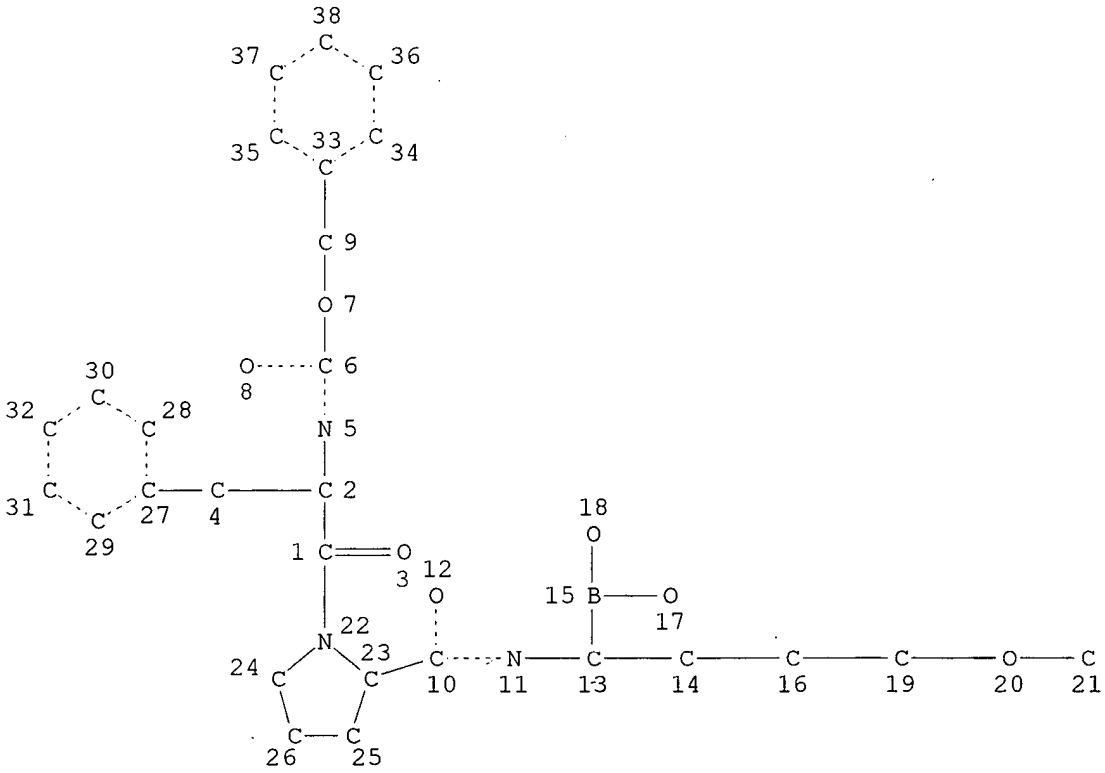

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NODE ATTRIBUTES:
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 38

STEREO ATTRIBUTES: NONE
L23 9 SEA FILE=REGISTRY SSS FUL L21
L24 3 SEA FILE=HCAPLUS L23

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L24 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:198296 HCAPLUS
DOCUMENT NUMBER: 140:229444
TITLE: Boronic acid salts and use thereof in the preparation of medicaments for treating thrombosis
INVENTOR(S): Madge, David Jonathan; Dolman, Mark; Combe-Marzelle, Sophie Marie; Deadman, John Joseph; Kennedy, Anthony James; Kakkar, Sanjay Kumar
PATENT ASSIGNEE(S): Trigen Limited, UK
SOURCE: Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1396270	A1	20040310	EP 2003-255629	20030909
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US 2004147453	A1	20040729	US 2003-659179 20030909
EP 1466916	A1	20041013	EP 2004-76510 20030909
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PRIORITY APPLN. INFO.:	GB 2002-20764	A 20020909
	GB 2002-20822	A 20020909
	GB 2003-7817	A 20030404
	GB 2003-11237	A 20030516
	GB 2003-15691	A 20030704
	US 2003-485786P	P 20030708
	EP 2003-255590	A3 20030909

OTHER SOURCE(S): MARPAT 140:229444

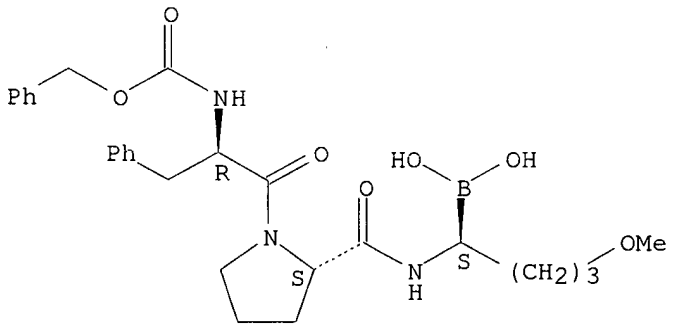
AB Salts of a peptide boronic acid drug, for example of Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)2 are described. The counter-ion to the boronate may be an alkali metal or derived from an organic nitrogen-containing compound The salts are used for the manufacture of a medicament for treating thrombosis.

IT **667917-16-0P**, TRI 50c
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation, antithrombotic activity, bioavailability and properties of oral boronic acid salts)

RN 667917-16-0 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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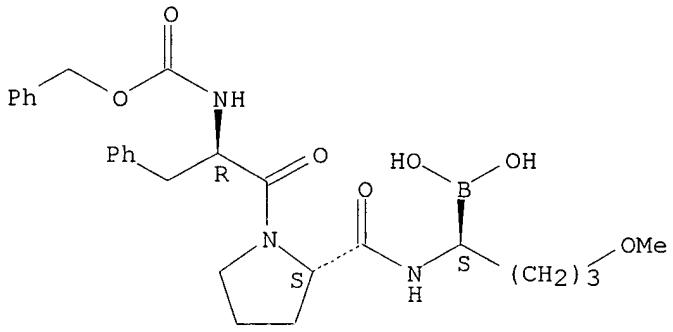
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation, antithrombotic activity, bioavailability and properties of oral boronic acid salts)

RN 667917-16-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 667917-80-8 HCAPLUS
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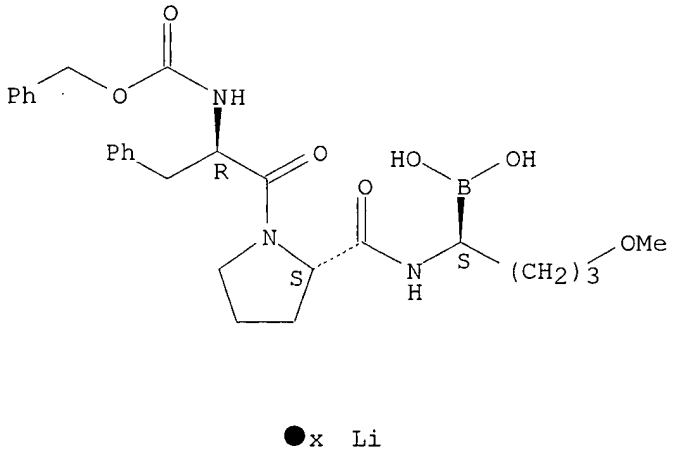
Absolute stereochemistry.



●x Li

RN 667917-82-0 HCAPLUS
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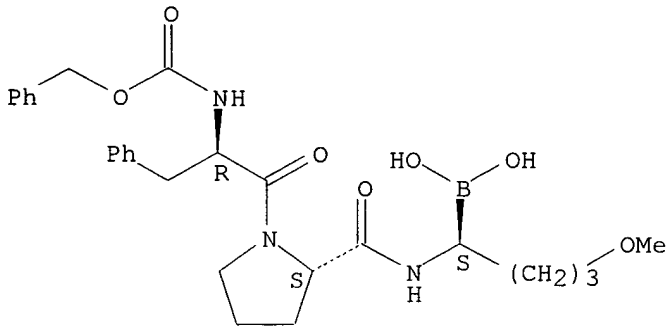
Absolute stereochemistry.



●x Na

RN 667917-83-1 HCAPLUS
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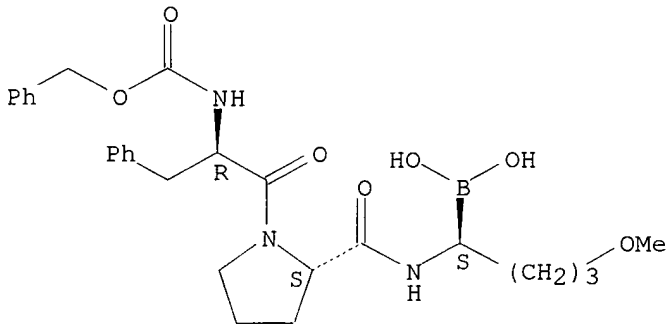
Absolute stereochemistry.



●x K

RN 667917-86-4 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, compd. with L-arginine (1:1) (9CI) (CA INDEX NAME)

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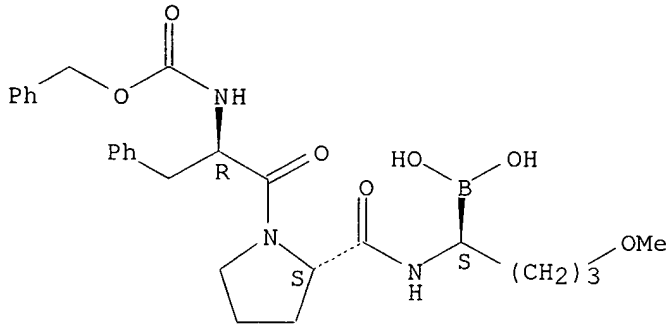
CRN 667917-16-0
CMF C27 H36 B N3 O7

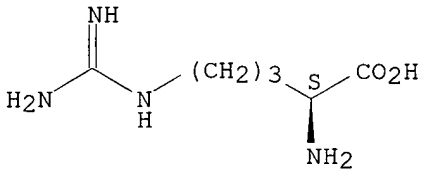
Absolute stereochemistry.



CM 2

CRN 74-79-3
CMF C6 H14 N4 O2

Absolute stereochemistry.



RN 667917-88-6 HCAPLUS
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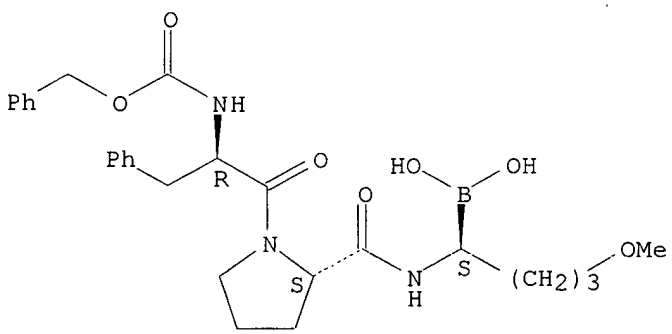
CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

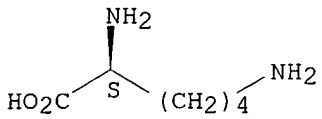
Absolute stereochemistry.



CM 2

CRN 56-87-1
CMF C6 H14 N2 O2

Absolute stereochemistry.

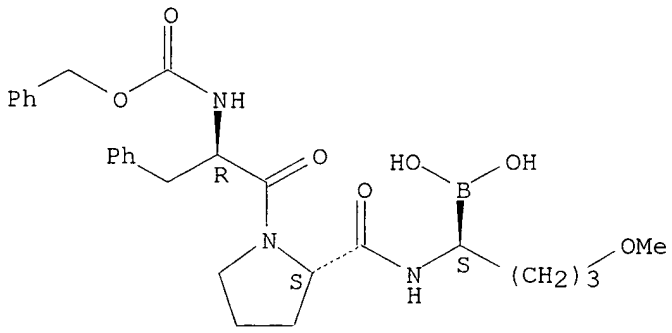


RN 667917-90-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, compd. with 2-deoxy-2-(methylamino)-D-glucose (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 667917-16-0
CMF C27 H36 B N3 O7

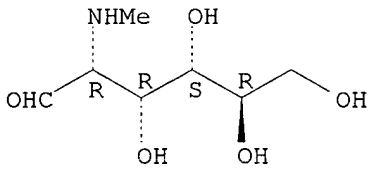
Absolute stereochemistry.



CM 2

CRN 3329-30-4
CMF C7 H15 N O5

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:198295 HCAPLUS
DOCUMENT NUMBER: 140:229443

TITLE: Boronic acid salts of multivalent metals used in the preparation of a medicament for treating thrombosis

INVENTOR(S): Madge, David Jonathan; Dolman, Mark; Combe-Marzelle, Sophie Marie; Deadman, John Joseph; Kennedy, Antony James; Kakkar, Sanjay Kumar; Chahwala, Suresh Babubhai; Boucher, Oliver Vimpany Arnold; Walter, Armin; Olbrich, Alfred; Krimmer, Dieter; Weiland-Weibel, Andrea Maria Theresia

PATENT ASSIGNEE(S): Trigen Limited, UK

SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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EP 1466917 A1 20041013 EP 2004-76521 20030909
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PRIORITY APPLN. INFO.: GB 2002-20764 A 20020909
GB 2002-20822 A 20020909
GB 2003-7817 A 20030404
GB 2003-11237 A 20030516
GB 2003-15691 A 20030704
US 2003-485786P P 20030708
EP 2003-255590 A3 20030909
OTHER SOURCE(S): MARPAT 140:229443

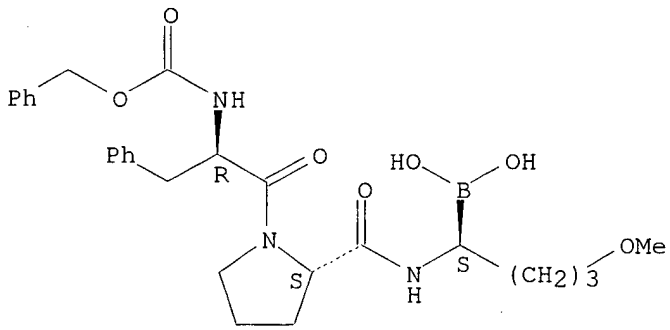
AB Salts of a pharmaceutically acceptable divalent metal and an organoboronic acid as selective thrombin inhibitors are described. Examples of such metals are calcium, magnesium and zinc. The organoboronic acid drug may be a boropeptide protease inhibitor. The salts may be formulated in oral dosage form, such as a capsule or compressed tablet.

IT **667917-16-0P**, TRI 50C
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation, antithrombotic activity, bioavailability and properties of oral boronic acid salts of multivalent metals)

RN 667917-16-0 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

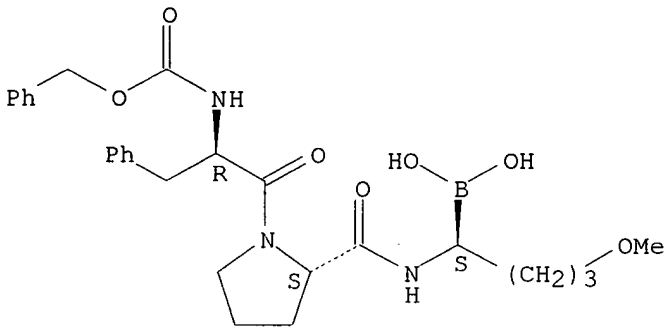


IT **667917-15-9P 667917-16-0DP**, Complexes with zinc or magnesium
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation, antithrombotic activity, bioavailability and properties of oral boronic acid salts of multivalent metals)

RN 667917-15-9 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]-, calcium salt (9CI) (CA INDEX NAME)

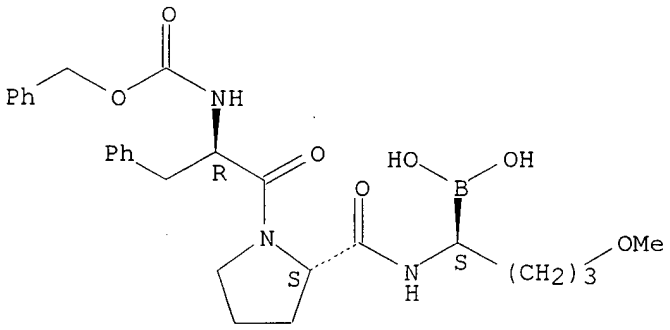
Absolute stereochemistry.



●x Ca

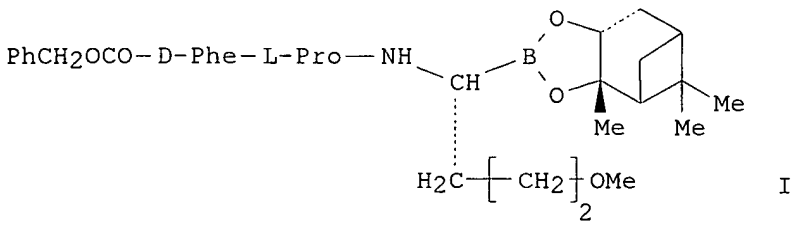
RN 667917-16-0 HCAPLUS
CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[(1S)-1-borono-4-methoxybutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:508296 HCAPLUS
DOCUMENT NUMBER: 122:281427
TITLE: Characterization of a Class of Peptide Boronates with Neutral P1 Side Chains as Highly Selective Inhibitors of Thrombin
AUTHOR(S): Deadman, John J.; Elgendy, Said; Goodwin, Christopher A.; Green, Donovan; Baban, Jehan A.; Patel, Geeta; Skordalakes, Emmanuel; Chino, Naoyoshi; Claeson, Goran; et al.
CORPORATE SOURCE: Thrombosis Research Institute, London, SM2 5TF, UK
SOURCE: Journal of Medicinal Chemistry (1995), 38(9), 1511-22
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

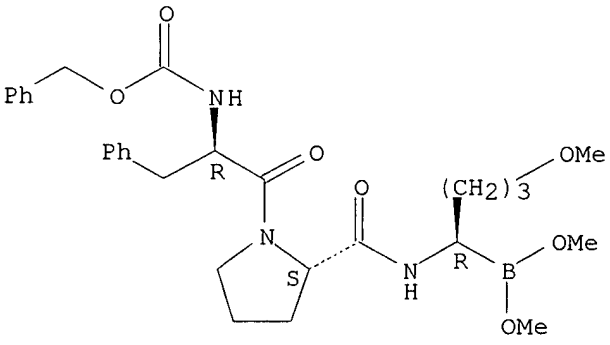
AB Z-D-Phe-Pro-boroMpg-OPin (I) has been shown previously to be a highly specific inhibitor of thrombin in spite of lacking an arginine-like guanidino group at the P1 site. A range of compds. have been synthesized based upon this lead compound, varying the neutral side chain at the P1 site. Of the 20 examples based upon the structures at P2 and P3 of Z-D-X-Pro (X being Phe or β,β-diphenylalanine), all were effective inhibitors of thrombin (Ki's between 10 and 100 nM). Furthermore all exhibited a high specificity toward thrombin having values for a Ki(trypsin)/Ki(thrombin) ratio of between 10- and 100-fold. High ratio values were found for a number of the compds. tested against a range of serine proteinases (plasmin, factor Xa, kallikrein, urokinase, protein Ca, chymotrypsin, elastase, and cathepsin G).2. As far as potency toward thrombin, compds. containing the methoxypropyl group at P1 were favored over those with a methoxy grouping on a shorter alkyl chain (8) or without the methoxy group (1-5). The compds. display potent anticoagulant activity with values for 18 in thrombin time of 0.63 μM and in activated partial thromboplastin time of 2.0 μM. 11B NMR has been used to confirm interaction of the boron atom with the active site. From the high specificity shown with all the compds., the authors propose that the compds., constitute a new class of thrombin inhibitors.

IT **162854-83-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(characterization of a class of peptide boronates with neutral P1 side chains as highly selective inhibitors of thrombin in relation to anticoagulant activity)

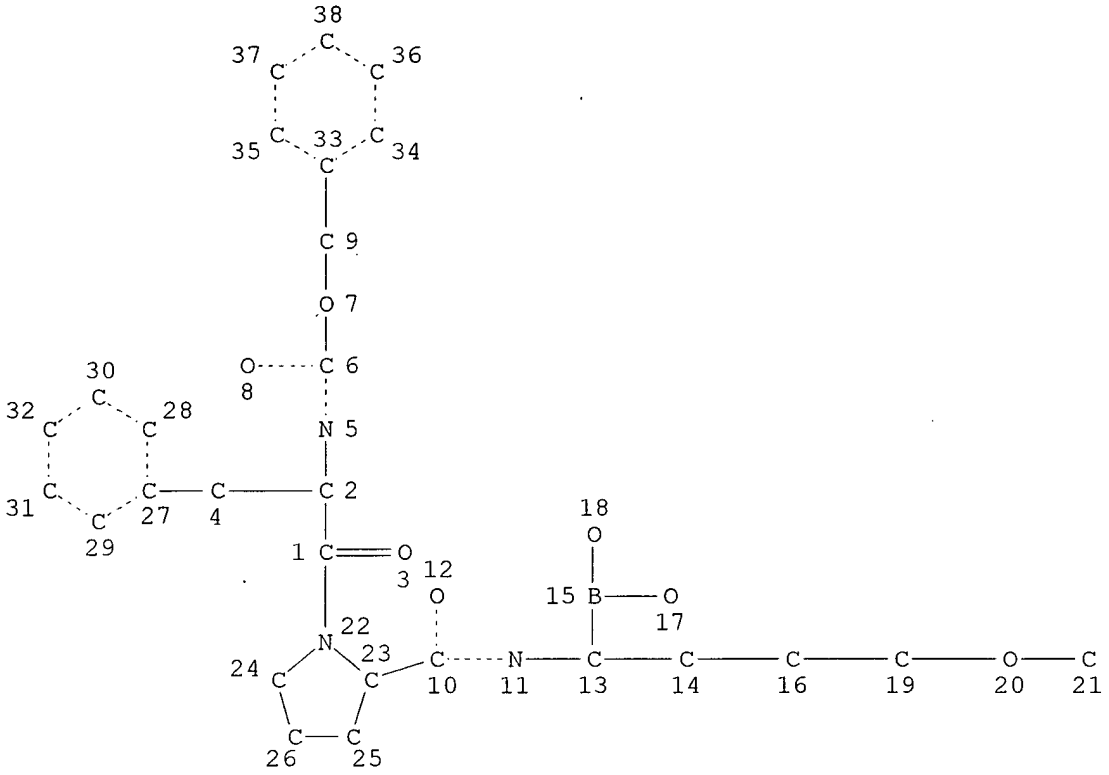
RN 162854-83-3 HCAPLUS

CN L-Prolinamide, N-[(phenylmethoxy)carbonyl]-D-phenylalanyl-N-[1-(dimethoxyboryl)-4-methoxybutyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> d que l32
L21 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 38

STEREO ATTRIBUTES: NONE

L23	9	SEA FILE=REGISTRY SSS FUL L21
L24	3	SEA FILE=HCAPLUS L23
L25	9551	SEA FILE=HCAPLUS INHIBIT?(5A)THROMBIN?
L26	81	SEA FILE=HCAPLUS L25 AND (BORON? OR ORGANOBORON?)
L27	6	SEA FILE=HCAPLUS L26 AND S1?
L28	3	SEA FILE=HCAPLUS L26 AND S2?
L29	3	SEA FILE=HCAPLUS L26 AND S3?
L30	1	SEA FILE=HCAPLUS L26 AND MULTIVALEN?(3A)METAL?
L31	9	SEA FILE=HCAPLUS (L27 OR L28 OR L29 OR L30)
L32	8	SEA FILE=HCAPLUS L31 NOT L24

=> d ibib abs l32 1-8

L32 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:186947 HCAPLUS

TITLE: Thrombin
AUTHOR(S): Rohde, Rosemary; Maderna, Andreas; Hawthorne, Fred
CORPORATE SOURCE: UCLA, Dept. of Chemistry, Los Angeles, CA, 90095, USA
SOURCE: Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), PRES-074. American Chemical Society: Washington, D. C.
CODEN: 69DSA4
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

AB Serine proteases constitute a major class of enzymes that are widely distributed in the human body. Examples of serine proteases are thrombin, trypsin, chymotrypsin, factor Xa, and human leukocyte elastase (HLE). Serine proteases are frequently the cause of many life-threatening diseases. Thrombin, for example, plays a central role in thrombosis and hemostasis. Thrombosis, or excessive blood clotting, is the major culprit of numerous cardiovascular diseases. Due to the high mortality rate of this disease and others, there is intensive interest in developing an orally active **thrombin inhibitor**. The goal of this work is to design and produce a selective and orally active **thrombin inhibitor** by synthesizing a **boronated** trans-lactum that will specifically bind to the active site of the enzyme. The **thrombin inhibitor** FE-1, composed of a trans-lactam template, a piperazinyl bisamide linker, and a hydrophobic carborane cage, was designed and optimized using mol. modeling and protein-ligand docking calcns. These techniques were utilized to determine the correct size, orientation, and stability needed for the inhibitor. FE-1 was synthesized in 22 steps and shown to have very good interactions with active site residues of thrombin: the Me groups on the carborane make lipophilic contact with the benzene ring to tryptophan 215 and isoleucine 174 and the **S3** pocket; the carbonyl group of the amide makes hydrogen bonds with the amino group of glycine 216; the piperazine ring has great contact with tyrosine 60A; and the trans-lactam template in its transition state is oriented in such a way that the OH group of serine 195 cleaves the amide bond of the lactam resulting in an intermediate tetrahedral carbon center in which the oxyanion group is place in the oxyanion hole of the S-1 site. All these interactions are extremely important in the development of thrombin-specific anticoagulants. In order to achieve an optically pure synthetic **thrombin inhibitor**, chiral HPLC was used in the final step of the reaction in order to sep. the correct a-diastereomer. This is unique and unprecedented mol. assemble represents an example of a new class of **boronated** enzyme **inhibitors** and yielded a new potential **thrombin inhibitor**. Partially funded by the ACS Scholars Program.

L32 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:354554 HCAPLUS
DOCUMENT NUMBER: 137:87844
TITLE: Design of Selective **Thrombin Inhibitors** Based on the (R)-Phe-Pro-Arg Sequence
AUTHOR(S): Danilewicz, John C.; Abel, Stuart M.; Brown, Alan D.; Fish, Paul V.; Hawkeswood, Edward; Holland, Stephen J.; James, Keith; McElroy, Andrew B.; Overington, John; Powling, Michael J.; Rance, David J.
CORPORATE SOURCE: Departments of Discovery Chemistry, Drug Metabolism, Discovery Biology, and Molecular Informatics Structure and Design, Pfizer Global Research and Development,

Sandwich, Kent, CT13 9NJ, UK
SOURCE: Journal of Medicinal Chemistry (2002), 45(12), 2432-2453
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:87844

AB Potent and selective **inhibitors** of **thrombin** were sought based on the (R)-Phe-Pro-Arg sequence. The objective was to generate similar binding interactions to those achieved by potent competitive inhibitors of the argatroban type, so eliminating the need for covalent interaction with the catalytic serine function, as utilized by aldehyde and **boronic** acid type inhibitors. Improving the **S1** subsite interaction by substitution of arginine with a 4-alkoxybenzamidine residue provided potent lead 2 (Ki = 0.37 nM). Though an amide bond, which H-bonds to the active site, is lost, modeling indicated that a new H-bond is generated between the alkoxy oxygen atom and the catalytic Ser-195 hydroxyl group. Substitution of the benzamidine system by 1-amidinopiperidine then gave compound 4, which provided a further gain in selectivity over trypsin. However, previous work had shown that these compds. were likely to be too lipophilic (log D +0.4 and +0.2, resp.) and to suffer rapid hepatic extraction, presumably via biliary elimination. Accordingly, both proved short-acting when administered i.v. to rats and showed poor activity when given intraduodenally. The aim was then to reduce lipophilicity below a log D of -1.2, which in a previously reported series had been effective in preventing rapid clearance. It was anticipated that compds. of this type would rely on the cation selective paracellular route of absorption from the gastrointestinal tract. Potent polar analogs with selectivity >1000 over trypsin were obtained. The best in vivo activity was shown by compound 12. However, in the final anal., its oral bioavailability proved poor, relative to analogs with similar physicochem. properties derived from argatroban, consistent with the hypothesis that mol. shape is an addnl. important determinant of paracellular absorption.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:619068 HCAPLUS
DOCUMENT NUMBER: 134:171
TITLE: Selective **boron**-containing **thrombin** **inhibitors**-X-ray analysis reveals surprising binding mode
AUTHOR(S): von Matt, A.; Ehrhardt, C.; Burkhard, P.; Metternich, R.; Walkinshaw, M.; Tapparelli, C.
CORPORATE SOURCE: Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: Bioorganic & Medicinal Chemistry (2000), 8(9), 2291-2303
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Based on the structural comparison of the **S1** pocket in different trypsin-like serine proteases, a series of Boc-d-trimethylsilylalanine-proline-boro-X pinanediol derivs., with boro-X being different amino **boronic** acids, have been synthesized as **inhibitors** of **thrombin**. Among the novel compds., a number of derivs. were synthesized which appeared to have side-chain variants too big to fit into

the **S1** pocket. Nevertheless, these compds. **inhibited thrombin** in the nM range. The x-ray structure of one of these inhibitors bound to the active side of thrombin reveals that a new binding mode is responsible for these surprising results.

REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:605764 HCAPLUS
DOCUMENT NUMBER: 129:341097
TITLE: Bifunctional Peptide **Boronate Inhibitors** of **Thrombin**: Crystallographic Analysis of **Inhibition** Enhanced by Linkage to an Exosite 1 Binding Peptide
AUTHOR(S): Skordalakes, Emmanuel; Elgendy, Said; Goodwin, Christopher A.; Green, Donovan; Scully, Michael F.; Kakkar, Vijay V.; Freyssinet, Jean-Marie; Dodson, Guy; Deadman, John J.
CORPORATE SOURCE: Peptide Synthesis Section and Biochemistry Section, Thrombosis Research Institute, London, SW3 6LR, UK
SOURCE: Biochemistry (1998), 37(41), 14420-14427
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The affinity of the hirudin49-64 segment for exosite 1 of thrombin has been used previously to enhance the potency of simple competitive inhibitors [DiMaio, J., Gibbs, B., Munn, D., Lefebvre, J., Ni, F., Konishi, Y. (1990) J. Biol. Chemical 265, 21698-21703, and Maraganore, J. M., Bourdon, P., Jablonski, J., Ramachandran, K. L., and Fenton, J. W., II (1990) Biochem. 29, 7095-7087]. Using a similar approach, we have enhanced the activity of two active site directed **thrombin inhibitors** by attaching this segment via a novel reverse oriented linker to each of two tripeptide **boronate** inhibitors. At P1, compound 1 contains an arginine-like, isothiouronium, side chain, while compound 2 contains an uncharged, bromopropyl residue. **Inhibition** of human α- **thrombin** by compound 1 shows slow, tight-binding competitive kinetics (final Ki of 2.2 pM, k1 of 3.51+107 M-1 s-1, and k-1 of 1.81+10-4 s-1). The addition of hirugen peptide (20 μM) competes for exosite 1 binding and restores the k1 and k-1 to that of the analogous tripeptide, 0.29+107 M-1 s-1 and 0.13+10-4 s-1, resp. Compound 1 has enhanced specificity for thrombin over trypsin with KiTry/KiThr of .apprx.900 compared to the analogous tripeptide, with KiTry/KiThr of .apprx.4. Compound 2 acts as a competitive inhibitor (KiThr of 0.6 nM) and is highly selective with no effect on trypsin. Crystallog. anal. of complexes of human α-thrombin with compound 1 (1.8 Å) and compound 2 (1.85 Å) shows a covalent bond between the **boron** of the inhibitor and Ser195 (bond lengths B-O of 1.55 and 1.61 Å, resp.). The isothiouronium group of compound 1 forms bidentate interactions with Asp189. The P2 and P3 residues of the inhibitors form interactions with the **S2** and **S3** sites of thrombin similar to other D-Phe-Pro based inhibitors [Bode, W., Turk, D., and Karshikov, A. (1992) Protein Sci. 1, 426-471.]. The linker exits the active site cleft of thrombin forming no interactions, while the binding of Hir49-64 segment to exosite 1 is similar to that previously described for hirudin [Rydel, T. J., Tulinsky, A., and Bode, W. (1991) J. Mol. Biol. 221, 583-601.]. Because of the similarity of binding at each of these sites to that of the analogous peptides added alone, this approach may be used to improve the inhibitory activity of all types of active site directed **thrombin**

inhibitors and may also be applicable to the design of inhibitors of other proteases.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:671089 HCAPLUS
DOCUMENT NUMBER: 127:341584
TITLE: Selection of **S18326** as a new potent and selective **boronic** acid direct **thrombin inhibitor**
AUTHOR(S): Rupin, A.; Mennecier, P.; Lila, C.; De Nanteuil, G.; Verbeuren, T. J.
CORPORATE SOURCE: Div. Angiology, Servier Research Inst., Suresnes, F-92150, Fr.
SOURCE: Thrombosis and Haemostasis (1997), 78(4), 1221-1227
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Using enzymic microassays, the potency of a series of new boroArg tripeptides was determined vs. thrombin and a panel of Ser proteases implicated in the coagulation and fibrinolysis pathways. The inhibition of the Ser protease complement factor I was also studied. Factor I regulates the alternate pathway of the complement and its inhibition appears to be responsible for the toxic effects of the orally available **thrombin inhibitor** Ac-D-Phe-Pro-boroArg (DuP-714). The structure of the new **boronic** acid derivs. tested was modified from that of DuP-714 by replacing the proline in the P2 position by N-cycloalkylglycine residues of increasing size (**S18989**: cyclopropyl; **S18563** : cyclobutyl; **S18326**: cyclopentyl; **S18229**: cyclohexyl). All compds. were found to be slow-tight binding **inhibitors** of **thrombin** vs. purified human fibrinogen. Replacement of Pro by N-cycloalkylglycines did not decrease the anti-thrombin potency of the substances up to the cyclopentyl size and this result was confirmed by classical coagulation assays with human plasma in vitro. In contrast, the inhibitory activities of the 4 new **boronic** acids were found to be lower than those of DuP-714 vs. plasmin, urokinase (u-PA), plasmatic kallikrein, activated protein C (aPC) and complement factor I. The cyclopentyl derivative **S18326** is a slightly more active **inhibitor** of **thrombin** than DuP-714 (initial IC50 values 3.99 nM vs. 4.73 nM, resp.). Moreover **S18326** was identified as the most selective compound of the series with relative potencies being 2-29-fold higher than that of DuP-714 vs. the panel of Ser -proteases tested; the rank order of potency vs. the other Ser proteases for **S18326** was t-PA > kallikrein > aPC > factor I > plasmin > fXa > u-PA. These results indicate that the size of the thrombin hydrophobic pocket **S2** is sufficient to accept larger residues than Pro in the P2 position of Ac-D-Phe-X-boroArg derivs. while this is not the case for other important Ser proteases of the fibrinolysis, coagulation, and complement pathways. The N-cyclopentyl glycine containing derivative **S18326**, which is the most potent and the most selective anti-thrombin compound of the series, currently undergoes major preclin. testing.

L32 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:667172 HCAPLUS
DOCUMENT NUMBER: 127:244735
TITLE: Crystallographic Structures of Human α-Thrombin

Complexed to Peptide **Boronic** Acids Lacking a Positive Charge at P1. Evidence of Novel Interactions

AUTHOR(S): Skordalakes, Emmanuel; Tyrell, Richard; Elgendy, Said; Goodwin, Christopher A.; Green, Donovan; Dodson, Guy; Scully, Michael F.; Freyssinet, Jean-Marie H.; Kakkar, Vijay V.; Deadman, John J.

CORPORATE SOURCE: Thrombosis Research Institute, London, SW3 6LR, UK

SOURCE: Journal of the American Chemical Society (1997), 119(41), 9935-9936
CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Moc-Dpa-Pro-boroMpg, compound (I), lacking a pos. charge at P1 is a potent **inhibitor** of human α- **thrombin** (Hαt) (KiThr = 3nM). The crystallog. anal. of the enzyme:inhibitor complex of I at 1.9Å resolution, provides for the first time a partial explanation for the basis of the high affinity interaction at the **S1** site. Tripeptide **boronates** I and Z-Dpa-Pro-boroVal, compound (II), were synthesized as described, and crystals obtained for I and II with HαT and N-Ac-hirugen. Crystals were flash cooled and data sets were collected to a maximum Bragg spacing of 1.8Å and 2.1Å resp. and subsequently processed with Denzo and Scalepack and AMORE (HαT.hirugen.PPACK). The data was further refined using Spartan, Refmac and ARP. Refinement converged to a crystallog. R factor of 17.5% (Rfree = 24.0%, using 5% of reflections) and 17.0% (Rfree = 23.5%) and R-factors were 0.32 and 0.36, and RMS deviations were 0.02Å and 2.4°, and 0.019Å and 2.5° for the complex with I and II, resp. Atomic coordinates have been deposited in the Brookhaven Protein Data Bank. Both compound I and II form the canonical interactions with human α-thrombin at the **S2** and **S3** sites, already shown with the PPACK complex. Complex I shows the expected covalent interaction of c.a. 1.75Å between the **boron** and the Ser-195Oγ of the HαT and O1B is coordinated by Gly-193NH and Ser-195NH in the so called oxy-anion pocket (Figure 1) (O1B-193GlyNH 2.79Å, O1B-ser195NH 3.11Å). In complex I, the ether oxygen is functioning as a hydrogen bond acceptor from a water (2.54 Å) which is, in turn, bridging to Gly-216CO and Gly-219CO. This bridging interaction has previously been observed in the fibrinopeptide A - α- thrombin complex, between the ε-NH of the arginine guanidino, WAT80 and Gly219CO. Surprisingly, despite the reasonable affinity of compound II, (Kithr 20nM), crystallog. anal. at 2.1Å of the complex II shows a novel interaction where the **boron** is 3.34Å from Ser-195Oγ, and the **boron** oxygen O1B is now displaced from the oxyanion pocket and is hydrogen bonded (2.84Å) to Ser-195Oγ. The displacement allows O1A to interact more strongly with the carboxylate side chain of Glu-192 (O1A-Glu192OE1 3.11Å compared to 4.16Å for complex II and I resp.). The inhibitor P1 valine-like iso-Pr side chain in complex II is displaced into close proximity with Val-213 of HαT. The discovery of this interaction between **S1** and **S3** for human α-thrombin may provide a better understanding for the design of low mol. weight inhibitors of high specificity.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:56330 HCAPLUS
DOCUMENT NUMBER: 126:139500

TITLE: **S1** heterocyclic **thrombin**

inhibitors

AUTHOR(S): Dominguez, C.; Carini, D. J.; Weber, P. C.; Knabb, R. M.; Alexander, R. S.; Kettner, C. A.; Wexler, R. R.

CORPORATE SOURCE: Exptl. Sta., DuPont Merck Pharmaceutical Co., Wilmington, DE, 19880-0500, USA

SOURCE: Bioorganic & Medicinal Chemistry Letters (1997), 7(1), 79-84
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of boropeptides have previously been described by Kettner et al. to be potent **thrombin inhibitors**. DuP 714 is a representative of this class of compds. with a Ki = 0.040 nM, but this inhibitor has undesirable side effects. New and selective **boronic** acid **thrombin inhibitors** have been developed by replacing the guanidine of the boroarginine side chain with various heterocycles ranging in size and basicity.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:413502 HCAPLUS

DOCUMENT NUMBER: 122:259717

TITLE: Kinetic and Crystallographic Studies of Thrombin with Ac-(D)Phe-Pro-boroArg-OH and Its Lysine, Amidine, Homolysine, and Ornithine Analogs

AUTHOR(S): Weber, Patricia C.; Lee, Sheng-Lian; Lewandowski, Francis A.; Schadt, Margaret C.; Chang, Chong-Hwan; Kettner, Charles A.

CORPORATE SOURCE: Chemical and Physical Sciences Department, The Du Pont Merck Pharmaceutical Company, Wilmington, DE, 19880-0228, USA

SOURCE: Biochemistry (1995), 34(11), 3750-7
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The x-ray crystallog. structure of Ac-(D)Phe-Pro-boroArg-OH (DuP714, Ki = 0.04 nM) complexed with human α-thrombin shows the **boron** atom covalently bonded to the side-chain oxygen of the active site serine, Ser195. The **boron** adopts a nearly tetrahedral geometry, and the **boronic** acid forms a set of interactions with the protein that mimic the tetrahedral transition state of serine proteases. Contributions of the arginine side chain to inhibitor affinity were examined by synthesis of the ornithine, lysine, homolysine, and amidine analogs of DuP714. The basic groups interact with backbone carbonyl groups, water mols., and an aspartic acid side chain (Asp189) located in the thrombin **S1** specificity pocket. The variation in inhibition constant by 3 orders of magnitude appears to reflect differences in the energetics of interactions made with thrombin and differences in ligand flexibility in solution Kinetic and crystallog. data are reported for the following **thrombin inhibitors**: DuP714 (space group C2, a = 70.8 Å, b = 72.3 Å, c = 72.6 Å, β = 100.6°, crystallog. R-factor = 0.204 to 1.95 Å resolution); Ac-(D)Phe-Pro-boroLys-OH (Ki = 0.24 nM, C2, a = 70.3 Å, b = 71.9 Å, c = 71.9 Å, β = 100.9°, R-factor = 0.201 to 2.35 Å resolution); Ac-(D)Phe-Pro-boro-homoLys-OH (Ki = 8.1 nM, C2, a = 70.3 Å, b = 71.9 Å, c = 71.9 Å, β = 100.9°, R-factor = 0.212 to 2.4 Å resolution);

Ac-(D)Phe-Pro-boroOrn-OH (Ki = 79 nM, C2, a = 70.4 Å, b = 72.2 Å, c = 72.2 Å, β = 100.1°, R-factor = 0.195 to 2.25 Å resolution); and Ac-(D)Phe-Pro-boro-n-butylamidinoGly-OH (Ki = 0.29 nM, C2, a = 70.8 Å, b = 72.4 Å, c = 72.2 Å, β = 100.3°, R-factor = 0.197 to 2.25 Å resolution).